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09/649,527	08/28/2000	Sean C. Semple	INEXP006US	8470

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OPPEDAHL AND LARSON LLP
P O BOX 5068
DILLON, CO 80435-5068

EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/649,527	Applicant(s) Semple
	Examiner Dave Nguyen	Art Unit 1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 7, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5-14, and 16-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5-14, and 16-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 4 and 15 have been canceled, claims 6, 17 have been amended by the amendment filed September 3, 2002 and the amendment filed January 7, 2003.

Elected claims 1-3, 5-14, 16-21, to which the following grounds of rejection remain applicable, are pending.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuation) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht,* 168 USPQ 293 (CCPA 1971). The parent application, 09/078,954, filed May 14, 1998, does not provide written support for the utility of any composition comprising a nucleic acid polymer and any cationic lipid within the context of immune-adjuvant for inducing an immune response against any desire molecule. While the '954 application provides sufficient guidance and teachings for the making of a DNA delivery composition comprising a cationic lipid and a DNA nucleic acid polymer, such description and/or contemplation of the making of DNA/cationic lipid composition for the purpose of using the composition simply as a DNA delivery composition is not the same as claiming now the **new property** and/or **new method** of any cationic lipid/DNA containing composition so as to induce a useful immune response against any desire antigen. Therefore, the parent application '954 application does not contain an adequate support of description the new property of immunostimulatory activity exhibited by any cationic lipid/DNA complexes which are essential for the practice of the claimed invention of this instant application, therefore priority for the claims readable on the conception of making and use of cationic lipid/DNA complexes as **immnostimulatory compositions within the context of adjuvants and/or inducer of an immune response** can only be established on the filing date of this instant application.

Applicant's response (dated January 7, 2003, pages 2 and 3) has been considered by the examiner but is not found persuasive for the reasons set forth above and the following reasons. Applicant mainly asserts that by merely reciting an "immunostimulatory composition" without reciting an intended use, the inherent properties of

the composition claims do not deprive the claims of the benefit of the priority date, and that examples 4, 9 and Figure 17 show "an increase in clearance rate when liposomes with oligonucleotide are administered in repeat doses, but no when empty liposomes are used". In response, the examiner maintains that applicant mischaracterizes the invention and its application of the antisense/cationic lipid in the parent case, *e.g.,* notably encapsulated DODMA/antisense and DODAP/antisense therapeutic composition. More particularly, Figure 17 and Example 4 of the parent case, when read as a whole, clearly teach that the encapsulated DODMA/antisense and DODAP/antisense therapeutic composition "appeared to be retained in the circulation to a degree which is suitable for human therapeutics". Figure 17 does not depict only an increase in clearance rate when any liposome with oligonucleotide is administered in repeat doses, but rather show a number of variations in clearance rate of a number of encapsulated cationic lipid/antisense containing formulations. In fact, Figure 17 coupled with the as-filed specification suggest that the lesser the clearance rate is for an encapsulated cationic lipid/antisense containing composition, the suitable it is for its intended application as a therapeutic when read within the teachings and contemplations as disclosed in the parent case. Neither Figure 17 nor example 4 nor example 9 teaches or suggests the ability of any **generic composition** comprising any generic nucleic acid polymer encapsulated in a cationic lipid containing lipid particle **to stimulate a useful and/or beneficial immunostimulatory response for any use within the context of 35 USC 101. On the contrary, the parent application, when read as a whole,** clearly envisions **the advantages in utilization of** encapsulated cationic amphiphile/**antisense** complexes **mainly by their lesser clearance response.** The intended application of an encapsulated cationic lipid/antisense DNA, as shown in Figure 17, examples 4 and 9 of the parent case, neither supports in any way a broader genus of any encapsulated cationic lipid/nucleic acid polymer complexes for use as an immunostimulatory composition, let alone other specific claimed limitations which recites CpG motifs and secretion of an cytokine, nor supports a method of employing any **generically encapsulated cationic lipid/biologically active nucleic acid polymer complex for the intended use as clearly claimed in claims 20 and 21, which claims are not even defined or supported in any way by the parent application of this as-filed application.**

Thus, the issue is whether or not a skilled artisan, on the basis of the parent application, would have recognized that applicant has possession of the full breadth of the claims subjected to an ongoing examination. As well-settled by precedent court decisions, *e.g., Burlington Industries, Inc. v. Quigg, 822 F.2d 1581, 1583, 3*

U.S.P.Q.2D (BNA) 1436, 1438 (Fed. Cir. 1987); In re Yamamoto, 740 F.2d 1569, 1571, 222 U.S.P.Q. (BNA) 934, 936 (Fed. Cir. 1984), the essential purpose of patent examination of any filed patent application is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process. In this instant case, applicant is seeking priority to generic claims that applicant defines as including the subject matter of an **immunostimulatory composition on the basis of the teaching provided by the parent application of this as-filed application .** However, not only the parent application does not provide any written support for any teaching that applicant's presently claimed subject matter which must exhibit the property of being immunostimulatory for any use as set forth in its teaching, the intended objective of increasing an immune response is precisely the response that the parent application identified as being disadvantageous when used in the context of a therapeutic. To prevail, applicant must show that applicant makes or possesses the subject matter that applicant is now claiming on the basis of applicant's disclosure at the time the invention was made.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-2, 6, and 20 are rejected under 35 U.S.C. 102(e) or 102(b) as being anticipated by Felgner *et al.* (US Pat No. 5,703,055), as evidenced by Bei *et al.* (J. Immunotherapy, 21, 3, pages 159-169, 1998)

The claims are readable on a method of employing any cationic amphiphile/biologically active molecule (DNA, RNA, polypeptides) contained composition regardless of the structure of the amphiphile and/or DNA so as to stimulate an immunostimulatory activity in a mammal. The '055 patent. discloses a method for generating an immunostimulatory

activity in a mammal by employing a cationic lipid/DNA complex, wherein said complex comprises a transduced vector or a polynucleotide expressing an antigen and any known cationic lipid/co-lipid complex, *e.g.,* DOTAP, columns 25 and 26. Delivery of the complex to tumor cell is disclosed on column 19, lines 40-45 and column 21, lines 21-26. Felgner *et al.* teach that "the polynucleotide material delivered to the cells *in vivo* can take any number of forms" (column 10). Suitable promoters, *e.g.*, RSV, SV40, and CMV, are disclosed on column 10. The polynucleotides can be delivered by injection to the interstitial space of tissues of the animal body, including those of muscle, skin, brain, lung, and connective tissues (see column 13). More specifically, the '055 patent teaches that "the parenteral route of injection into the interstitial space of tissues is preferred, although other parenteral routes, such as inhalation of an aerosol formulation, may be required in specific administration, as for example to the mucous membranes of the nose, throat, bronchial tissues or lungs" (column 24). Felgner *et al.* disclose that "the polynucleotides may be injected into muscle or skin using an injection syringe...or...using a vaccine gun" (column 20). Regarding the DNA injection methods using a cationic lipid, Felgner *et al.* teach many suitable liposome forming cationic lipid compounds for use in the transient gene therapy method are described in the literature and available commercially (column 26). Specific examples demonstrating an antibody immune response against an antigen are disclosed in Examples 7-16 (tail vein injections, direct injection into the muscle, intratracheal and liver injections). Methods employing intravenous injections of a cationic lipid/DNA complex to deliver biologically active molecules including an interferon gene to human patients are disclosed at column 18, first paragraph.

Since the cationic lipid/DNA complexes, *e.g.,* well-known encapsulation technique is disclosed on last paragraph of column 24, and/or materially method steps of Felgner are identical to that of the claims of this instant application, and given the factual evidence shown by the Bei reference which indicates that cationic liposomes formulation (DOTAP) does stimulate immune responses and are themselves immunoadjuvant (entire document, especially the abstract), the cationic lipid/DNA complexes including the DOTAP lipid/DNA composition of Felgner *et al.* must inherently exhibit the property of immunostimulatory activity in a mammal.

Applicant mainly asserts (pages 3 and 4 of the response) that Felgner does not teach encapsulation, that not only the prior art does not teach an encapsulated lipid particle comprising a cationic lipid encapsulating any nucleic acid polymer, applicant were the first one who discovered the make and use of such lipid particle. The examiner maintains that the prior art of record including Felgner and Wheeler, when read as a whole, disproves applicant's assertion. In particular, column 24 of Felgner states:

The science of forming liposomes is now well-developed. Liposomes are unilamellar or multilamellar vesicles, having a membrane portion formed of lipophilic material and an interior aqueous portion. The aqueous portion is used in the present invention to contain the polynucleotide material to be delivered to the target cell. It is preferred that the liposome forming materials used herein have a cationic group, such as a quarternary ammonium group, and one or more lipophilic groups , such as saturated or unsaturated alkyl groups having from about 6 to 30 carton atoms.

As such, one of ordinary skill in the art would have recognized that at the time the invention was made, it is well-accepted within the scientific community and the level of a person of ordinary skill in the art to make and use a liposomal particle comprising a cationic lipid, which encapsulates a nucleic acid polymer. This concept of encapsulating biologically active molecules including negatively charged DNA by using a cationic liposome is further illustrated on column 10 of US Pat No. 6,110,490, entire disclosures of US 2002/0192651 (Wheeler II), US 5,976,567 (Wheeler I), WO 96/40964 (Wheeler III), and Bailey (US 5,552,155). The fact that applicant now recognizes the novel properties of any cationic lipid is irrelevant since a claim directed to an old product where a discovery of a new property or a new use of an old product is not patentable. Note that MPEP 2114 indicates that "MANNER OF OPERATING THE DEVICE DOES NOT DIFFERENTIATE APPARATUS CLAIM FROM THE PRIOR ART".

Claims 1-3, 5, 9-14, 16, 20, 21 are rejected under 35 USC 102(a) or 102(e) as being anticipated by Krieg *et al.* (US Pat No. 6,207,646).

The essential feature of the presently pending claims is that any cationic lipid including can be used for a method of inducing an immune response when used in combination with a nucleic acid polymer including those containing CpG motifs which themselves are also immunostimulatory nucleic acid molecules. Krieg *et al.* teach that cationic lipid carriers (column 12, lines 25-34) can be employed in combination with a CpG motif containing nucleic acid polymer as immunostimulatory nucleic acid complex and with an antigen when employed for induction of an immune

response to a target antigen. The 646 patent teach the same throughout the disclosure (particularly columns 29-35, columns 61-64).

Absent evidence to the contrary, the compositions and the methods disclosed in Krieg *et al.* have all of the properties cited in the claims.

Applicant (page 4 of the response) asserts that Krieg does not teach specifically an encapsulation of DNA in a cationic lipid containing lipid particle. In response, the examiner maintains that while Krieg does not state the exact phrase as recited in the claims, Krieg states on column 12:

> An "oligonucleotide delivery complex" shall mean an oligonucleotide associated with (e.g. ionically or covalently bound to; or encapsulated within a targeting means (e.g. a molecule that results in higher affinity binding to target cell (e.g. B-cell and natural killer NK) cell) surfaces and/or increased cellular uptake by target cells). Examples of oligonucleotide delivery complexes include oligonucleotides associated with: a sterol (e.g. cholesterol), a lipid (e.g. a cationic lipid, virosome or liposome), or a target cell specific binding agent (e.g. a ligand recognized by target cell specific receptor). Preferred complexes must be sufficiently stable in vivo to prevent significant uncoupling prior to internalization by the target cell. However, the complex should be cleavable under appropriate conditions within the cell so that the oligonucleotide is released in a functional form.

As such, Krieg does teach that his CpG containing nucleic acid polymer or oligonucleotide can be encapsulated within an oligonucleotide delivery complex, and that the complex includes a cationic lipid-based lipid. While Krieg does not teach detailed description of a method of how to make such oligonucleotide delivery lipid that encapsulates a CpG containing oligonucleotide, such method is well-recognized in the prior art as being routine and conventional, as evidenced by the a teachings provided by Felgner, Wheeler I, and Wheeler II, Wheeler III and Bailey.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-14, and 16-21 are rejected under 35 USC 103 as being unpatentable over Felgner *et al.,* taken with either Meers *et al.* (US Pat No. 6,143,716) or Wheeler *et al.* (US Pat No. 5,976,567), and further in view of applicant's admission over the prior art on pages 7 and 11 of the specification.

The rejection of the base claims as being anticipated by Felgner is applied here as indicated above. To the extent that the references do not teach further incorporations of known components (see pages 7 and 11 of the specification, for example) for additive effects, *e.g.,* CpG containing motifs with proper flanking residues that contributes to the immunostimulatory effects, steric barrier lipid (PEG-lipid), drugs, cytotoxic agents, modified DNA with phosphodiester bonds, and/or recombinant antigen, or antigen encoded plasmids, it would have been obvious for one of ordinary skill in the art as a matter of design choice, of minor modifications, or of a combination effect, to employ any and/or all other components are recited in the claims, *e.g.,* CpG containing motifs with proper flanking residues that contributes to the immunostimulatory effects, steric barrier lipid (PEG-lipid), drugs, cytotoxic agents, modified DNA with phosphodiester bonds, and/or recombinant antigen, or antigen encoded plasmids in the immunogenic compositions of any of the primary references. One of ordinary skill in the art would have been motivated to employ known immunostimulatory and/or therapeutic enhancing materials in the prior art so as to enhance addictive effects of the compositions taught in the primary references. Note that Krieg (WO 96/02555) as exemplified on page 7 of the specification, does teach the concept of adding known immunostimulatory materials including CpG motif containing oligos and/or recombinant antigens to known plasmid DNA vaccines is well established in the prior art of record. In addition, note also that Meers *et al.* teach on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.,* drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal.

The skilled artisan would also have been motivated to employ any known cationic lipid including DODMA and DODAP/PEG-lipid/DOPE as the lipid of choice for encapsulating any nucleic acid plasmid disclosed in Felgner because not only the primary references teach that cationic lipids are effective encapsulating delivery liposome, Wheeler *et al.* (column 50, example 26) and Meers *et al.* also teach that DODMA and DODAP/PEG-lipid/DOPE, respectively, are also effective as a vector for delivering and expressing any desire DNA in cells of a mammal. Note also that Meers *et al.* teach on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.,* drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal. Thus, an addition of well-recognized immune-stimulating agents including those of protein drugs to the teachings provided by the combined cited references would have been minor modifications so as to provide addictive or combination effects, and thereby, would have been obvious to one skilled in the art at the time the invention was made.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant mainly asserts in the latest response that the primary reference does not teach the "encapsulating" limitation, however, the examiner maintains that applicants were not the first to discover the "encapsulating" lipid being used as a lipid carrier, such is well known and conventional in the prior art including both of the cited Felgner and Wheeler. Applicant further argues about the unexpected result of the cationic lipid/DNA carrier, the examiner maintains that let alone the fact that applicant has not provided any factual evidence to reasonably extrapolate from the exemplified cationic lipid/DNA based carriers to the full scope of the claimed subject matter, the combined cited references does teach and suggest a motivation to employ DODMA or DODAP/PEG-lipid/DOPE as an effective encapsulated lipid carrier for any biologically active molecule including the DNA based plasmids disclosed in Felgner, whereby the delivery efficacy of employing such lipid based carrier is not considered as being unexpected by a person of ordinary skill in the art at the time the invention was made, particularly on the basis of the teachings provided by the totality of the prior art of record. The fact applicant may have a <u>different</u> motivation to employ DODMA or DODAP/PEG-lipid/DOPE as an enhancer for an *in vivo* secretion of cytokines does not negate the teaching provided by the combined cited references, which, when read as a whole, would lead one person of ordinary skill in the art, with a

reasonable expectation of success, to make and use the very same claimed compositions as effective *in vivo* lipid based carriers for the plasmid DNA of Felgner.

Claims 1-3, 5-14, and 16-21 are rejected under 35 USC 103 as being unpatentable over Krieg *et al.* (US Pat No. 6,207,646), taken with either McCluskie *et al.* (Critical Reviews in Immunology, 19, pp. 303-329, 1999), and further in view of either Wheeler *et al.* (US Pat No. 5,976,567) or Meers *et al.* (US Pat No. 6,143,716).

The essential feature of the presently pending claims is that any cationic lipid including can be used for a method of inducing an immune response when used to encapsulate a nucleic acid polymer including those containing CpG motifs which themselves are also immunostimulatory nucleic acid molecules. Krieg *et al.* teach that cationic lipid carriers (column 12, lines 25-34) can be employed in combination with a CpG motif containing nucleic acid polymer as immunostimulatory nucleic acid complex and with an antigen when employed for induction of an immune response to a target antigen. The 646 patent teaches the same throughout the disclosure (particularly columns 29-35, columns 61-64).

Krieg does not teach specifically that the liposomal vesicles contain a particular cationic lipid such as DODMA or DODAP and/or PEG-lipid as stabilizer for the nucleic acid delivery complexes.

However, at the time the invention was made, McCluskie *et al.* (page 307 through page 308) do teach that cationic lipids, which themselves are effective conventional carriers for enhancing the delivery and expression of a target nucleic acid polymer, can also be used as effective adjuvant for the purpose of inducing an immune response against a target antigen.

In addition, Wheeler *et al.* and Meers *et al.* do teach that DODMA (column 50, example 26) and DODAP/PEG-lipid/DOPE (columns 8 and 9), respectively, also effective carriers for delivering and expressing any desire DNA molecule in a mammal.

One of ordinary skill in the art would have been motivated to have employed a cationic lipid including DODMA or DODAP on the basis of teaching provided by Wheeler or Meers in the method of Krieg so as to enhance an immune response against a target antigen. One of ordinary skill in the art would have been motivate to employ a cationic lipid as an adjuvant and/or a based lipid carrier because McCluskie *et al.* (page 307 through page 308) do teach that cationic lipids, which themselves are effective conventional carriers for enhancing the delivery and expression of a target nucleic acid polymer, can also be used as effective adjuvant for the purpose of inducing an immune response against a target

antigen. The skilled artisan would also have been motivated to employ any known cationic lipid including DODMA and DODAP/PEG-lipid/DOPE as the lipid of choice because not only the combined cited references teach that cationic lipids are effective immuno-adjuvants, Wheeler *et al.* and Meers *et al.* also teach that DODMA and DODAP/PEG-lipid/DOPE, respectively, are also effective as a vector for delivering any desire DNA in cells of a mammal. Note also that Meers *et al.* teach on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.,* drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal. Thus, an addition of well-recognized immune-stimulating agents including those of protein drugs to the teachings provided by the combined cited references would have been minor modifications so as to provide addictive effects, and thereby, would have been obvious to one skilled in the art at the time the invention was made.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant (pages 5 and 6) further asserts about the priority issue, which was already discussed *supra.* Note also that no where in the parent application of this as-filed specification, there is any written support for the method as claimed in claims 20 and 21, and for the limitation of "immunostimulatory" and/or "CpG motif". Applicant further asserts that since the secondary references are limited to the use of encapsulated lipid carriers to deliver an expressible DNA, it is inappropriate to combine with the primary reference in order to arrive at the invention as claimed, and that the primary reference is limited only to non-expressible oligonucleotide. In response, the examiner maintains that insofar as the Krieg reference clearly teaches that any available delivery complex composed of a cationic lipid can be used as an encapsulating delivery complex for delivering Krieg's oligonucleotide, one of ordinary skill in the art would have been motivated to employ the DODMA and DODAP/PEG-lipid/DOPE of Wheeler or Meers as an encapsulating lipid delivery vector, since both references do teach that DODMA and DODAP/PEG-lipid/DOPE are effective delivery lipid-based carriers, and that the lipid carriers are not limited solely for use in expressing only expressible DNA such as a plasmid DNA vector.

For example and in particular, Wheeler on column 11, last paragraph, clearly teaches that the nucleic acids are typically nucleotide polymers having from 10 to 100,000 nucleotide residues, and that the nucleic acids include oligonucleotides containing nucleic acid analogs, and that the nucleic acids can be single-stranded DNA. Thus, to the extent that applicant asserts that the combination of the cited references is an improper combination, the assertion is not found persuasive. In summary, the first issue is whether or not the prior art of record teaches an encapsulating lipid carrier. The stated rejections of record do provide evidentiary support to demonstrate that

the concept of making an encapsulating lipid carrier as an oligonucleotide delivery complex is routine and conventional in the prior art of record. The second issue is whether or not a skilled artisan would have been motivated to employ the DODMA and DODAP/PEG-lipid/DOPE of Wheeler or Meers as an encapsulating lipid delivery vector. Again, the stated rejection of record does teach, suggest, and provide a motivation for a skilled artisan to employ the DODMA and DODAP/PEG-lipid/DOPE of Wheeler or Meers as an encapsulating lipid delivery vector to deliver the oligonucleotide of Krieg. The third issue is the priority issue. Again, in view of the fact and reasons set forth in the above preceding paragraphs, not only a skilled artisan would have recognized that applicant, at the time the parent application of this instant application was filed, was not contemplating a generic invention of using any cationic lipid based lipid particle as an immunostimulatory agent, was not contemplating of using specifically just a CpG containing nucleic acid polymer as an immunostimulatory agent, was not contemplating a specific combination of any immunostimulatory cationic lipid based lipid and specifically a CpG containing nucleic acid polymer, a skilled artisan would have recognized, on the basis of the parent application, that the intended application of an encapsulated cationic lipid/antisense DNA, as shown in Figure 17, examples 4 and 9 of the parent case, neither supports in any way a broader genus of any encapsulated cationic lipid/nucleic acid polymer complexes for use as an immunostimulatory composition, let alone other specific claimed limitations which recites CpG motifs and secretion of an cytokine, nor supports a method of employing any generically encapsulated cationic lipid/biologically active nucleic acid polymer complex for the intended use as clearly claimed in claim 20 and 21, which claims are not even defined or supported in any way by the parent application of this as-filed application.

To further respond to applicant 's assertion that the concept of employing cationic lipid based encapsulation of nucleic acid is not well-known at the time the invention was made, the following references, in addition to the already cited Wheeler I, Wheeler II, Wheeler III and Bailey, are cited to further demonstrated that it is well recognized within the scientific community that it is conventional in the prior art to encapsulate biologically active molecules including negatively charged DNA by using a cationic liposome:

McEver (US Pat No. 5,605,821, first full paragraph of column 21); Chang (US 2002/0162123, Boulikas (US Pat No. 6,030,956, column 13).

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUORY PERIOD FOR RESPONSE EXPIRE LATER THAN **SIX MONTHS** FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER